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Post-marketing safety surveillance for inactivated Enterovirus 71 vaccines in Jiangsu, China from 2017 to 2019

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ABSTRACT

Introduction: Two types of enterovirus 71 (EV71) vaccines, manufactured using human diploid (H2) and Vero cells, have been administered in Jiangsu Province, China since 2017. In this study, we evaluated their safety profiles using records collected from the Chinese National Adverse Events Following Immunization (AEFIs) Information System (CNAEFIS) and Electronic Immunization Registries System (EIRS) between 2017 and 2019.

Methods: Demographic characteristics of the patients, AEFI incidence rates(IRs), symptoms, and time intervals were summarized from the reported AEFI data in the CNAEFIS. Also, the administered doses of the two vaccines were exported from the EIRS to calculate the IRs of AEFIs and thus compare the AEFIs between the two types of EV71 vaccines.

Results: In total, 209, 407, and 344 AEFIs cases following EV71 vaccine administration were reported during 2017, 2018, and 2019, respectively, yielding IRs of 59.2, 48.2, and 54.2 per 100,000 doses, respectively. Fever, irritability, allergic eruptions, fatigue, loss of appetite, redness and induration at the injection site were the most commonly reported AEFIs. No significant differences in rare reactions were found between the two types of EV71 vaccinations. The majority of AEFIs were developed within 30 min to 3 days after administration.

Conclusion: EV71 vaccines showed satisfactory safety profiles since their first use 3 years ago in the Jiangsu Province. The AEFI profiles were identical to those in pre-marketing studies; most AEFIs after vaccination were mild and common. More active surveillance studies should be performed to provide more comprehensive post-marketing safety data.

1. Introduction

Hand, foot, and mouth disease (HFMD) is an acute viral skin disease primarily observed in children under the age of 5 years [1,2]. As an infectious disease caused by a group of enteroviruses, HFMD is a serious public health problem in countries in the Western Pacific region [3,4]. From May 2008 to March 2015, approximately 13 million cases of HFMD were reported in mainland China, of which 3,322 were fatal [5]. Although most of the HFMD cases are mild and self-limited, some cases can develop serious complications, such as meningitis, encephalitis, and even death. Enterovirus 71 (EV71) is the pathogen that causes HFMD and can cause various other diseases, including herpangina and aseptic meningitis and a few nonspecific illnesses [6,7]; EV71 accounts for 70% of severe HFMD cases and 90% of HFMD-related deaths [8]. However, to date, no effective drugs for the treatment HMFD have been developed.

To reduce the tremendous burden on public health caused by HFMD epidemic and EV71 morbidity, EV71 vaccination is required in Asian countries. By December 2015, two types of the inactivated EV71 vaccines have been approved for marketing in China by the China Food and Drug Administration (CFDA) [9]: the inactivated EV71 vaccine derived from human diploid (H2) cells and inactivated EV71 vaccine derived from Vero cells. Both inactivated EV71 vaccines are developed with the use of C4 genotype strain, the predominant strain circulating in Chinese mainland. In clinical trials, two types of the EV71 vaccines displayed adequate safety, immunogenicity, and efficacy [10]. Although the EV71 vaccines are not included in the Expanded Programme on Immunization (EPI) in China, increasing awareness and acceptance of the EV71 vaccine in parents has been observed [11]. For newly approved vaccines, evaluation of safety in much larger target population is required to obtain comprehensive post-marketing safety data, according to the recommendations of the World Health Organization [12] and CFDA. Nevertheless, safety data for the EV71 vaccines have been mainly obtained from phase I–III clinical trials. Thus, post-marketing studies of the safety of EV71 vaccines are still

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lacking. In China, vaccine safety monitoring in post-marketing surveillance primarily relies on a passive reporting system called the Chinese National Adverse Events Following Immunization Information System (CNAEFIS) [13]. In this system, an Adverse Events Following Immunization (AEFI) case is defined as a reaction or event following vaccination, suspected to be related to the vaccine infusion; AEFI surveillance covers all vaccines marketed in mainland China. More than 90% of the counties in China have reported AEFIs to CNAEFIS since 2013. Because the Chinese individual-level Electronic Immunization Registries System (EIRS) is not available presently [30], CNAEFIS data uses the reported vaccine administration dose as a denominator when calculating the incidence rates(IRs) of AEFIs. However, the use of the reported doses is not sufficient for performing detailed and accurate analyses. For example, it is not possible to analyze and directly compare the actual IRs of AEFIs between different types of EV71 vaccines, ages, and sexes et al.

Jiangsu Province is located in the eastern part of China and has a population of 80 million people. In the last decade, rapid progress has been made in developing a provincial-level EIRS in Jiangsu Province [14]. Electronic information of children and vaccine are required to input into the EIRS by the doctors providing immunizations.

Accordingly, in order to provide a comprehensive analysis of the safety of EV71 vaccines, we conducted a post-marketing observational study, based on data from the CNAEFIS and EIRS in Jiangsu Province, China, from 2017 to 2019.

2. Methods

2.1. Vaccination schedule for EV71 vaccines

The H2 cell-based inactivated EV71 vaccine was administered to children aged from 6 months to 5 years old, whereas the Vero cell-based inactivated EV71 vaccine was administered to children aged from 6 months to 3 years old. Both types of EV71 vaccines were administered via the intramuscular route using a two-dose schedule at an interval of one month.

2.2. Surveillance of CNAEFIS

Since 2008, the CNAEFIS has been managed by the Chinese Center for Disease Control and Prevention (CDC), according to China's national AEFI guidelines [15]. AEFIs are defined as unexpected harmful reactions or reactions unrelated to the expected purpose of the vaccine that occur after standard vaccination. AEFIs can be classified into five types. Type 1, Vaccine product-related reaction, is defined as reactions unrelated to the expected purpose of the vaccination that occur after standard infusion with a vaccine product, including common adverse reactions and rare adverse reactions. Common adverse reactions are caused by the inherent characteristics of the vaccine after infusion, and they impair body functions in a transient manner; these adverse reactions mainly include fever and localized redness and swelling, accompanied by discomfort, fatigue, and loss of appetite. Rare adverse reactions are defined as adverse reactions occurring during the process of vaccine administration or after vaccination with a standard vaccine that damages tissues or organs and the normal functioning of the vaccine recipient. Type 2, Vaccine quality event, is defined as damage to tissues or organs and damage to the normal functioning of the vaccinated person due to substandard quality of the vaccine. Type 3, Program error, is the damage to tissues or organs and to normal functioning of the vaccine recipient due to violation of standard operational practices, vaccination procedures, or guidelines for using the vaccine. Type 4, Coincidental event, are when the vaccine recipient is in the incubation stage or preclinical stage of a certain condition, and the onset of the disease coincides with the vaccination. Type 5, Psychogenic reaction, is the individual reactions or reactions of groups of individuals that occur during or after the vaccination due to the psychological responses of the recipients.

Since 2010, all healthcare facilities, vaccination clinics (VCs), the CDC, adverse drug reaction (ADR) monitoring agencies, and the executive staff of vaccine manufacturers in Jiangsu Province are required, by law, to report AEFI cases. The public or children's parents (or guardian) can notify any of the above authorized agencies to report an AEFI case. In Jiangsu, after finding AEFI cases, all the above authorized agencies should report it to the VC or the county-level CDC where the VC is located; the VC or the county-level CDC then completes the "AEFI Case Reporting Cards" and submits the data to CNAEFIS. Once the information is inputted into CNAEFIS, it can be viewed by all administrative levels of CDCs and ADRs. Investigation and diagnosis are required for all AEFIs, except common adverse reactions with a clear diagnosis. For deaths, serious AEFIs, AEFI clusters, and AEFIs causing significant public concern and are suspected to be related to vaccination, prefectural or provincial CDCs must immediately organize an AEFI expert panel for investigation upon receiving CNAEFIS reports.

2.3. Information on AEFIs

AEFIs occurring after the administration of the EV71 vaccines in the Jiangsu Province, since the vaccines were marketed, from January 2017 to November 2019 were reviewed. AEFI data that were extracted from the CNAEFIS during the above period were included in this study for cases in which any type or dose of an EV71 vaccine was administered. When more than one symptom was reported for a case, each symptom, investigation, and diagnosis was recorded by the CNAEFIS. The following AEFI data were included from the reported cases: demographic information of the patient experiencing the AEFI, vaccination information, vaccination date, lot number, co-administered vaccines, symptoms, diagnosis, classification of the AEFI, case severity, and prognosis.

2.4. Number of EV71 vaccine doses

The number of EV71 vaccine doses, which was extracted from the provincial central server database of EIRS in Jiangsu Province, was selected as a denominator to calculate the IR of the AEFI. When children received any type of vaccine at a VC in Jiangsu Province, the name, birth date, home address, and vaccination information (e.g., vaccine name, type, lot number, and dose number) were submitted to EIRS by the doctors administering the vaccine and automatically uploaded to provincial central servers.

2.5. Statistical analysis

Age, sex, classifications of AEFI, and clinical symptoms, the EV71 vaccine type, and year of reporting were evaluated. AEFI IRs per 100,000 doses of vaccine administered were calculated for total case reports and for each AEFI classification. Incidence rate ratios (IRRs) with 95% confidence intervals (95% CIs) were used to compare the IRs of different AEFIs against EV71 vaccines derived from H2 and Vero cells. All data analyses were performed using Microsoft Excel 2010 and SPSS 18.0 software (IBM, Armonk, NY, USA).

3. Results

In total, 1.8 million doses of the EV71 vaccines were administered from January 2017 to December 2019; of these,

approximately 1.2 million were H2 cell-based EV71 vaccines, and 0.6 million were Vero cell-based EV71 vaccines, as recorded in the EIRS. In total, 209, 407, and 344 AEFIs cases following EV71 vaccine administration were reported during 2017, 2018, and 2019, respectively, yielding IRs of 59.2, 48.2, and 54.2 per 100,000 doses, respectively. Table 1 illustrates the characteristics of AEFIs after vaccination. The AEFI IR related to the EV71 vaccines was higher in boys than in girls, and the IR sex ratio was 1:0.8. The IR of AEFIs in children 1–2 years old was higher than that in other age groups. Additionally, more AEFIs were reported for patients receiving the first dose than for those receiving the second dose. In particular, the AEFI IRs after administration of the Vero cell-based EV71 vaccine decreased over time from 2017 to 2019, and the IRs of both type of EV71 vaccines were similar.

Most AEFIs following administration of EV71 vaccines were common reactions; and rare reactions and coincidental events only accounted for 12.2% and 1.1% of cases, respectively. No vaccine quality events, program errors, psychogenic reactions, or deaths were reported. The IRRs analysis indicated no differences in rare reactions and coincidental events between the two types of vaccines. The IRs of AEFIs defined as common reactions were higher for Vero cell-based EV71 vaccines than H2 cell-based EV71 vaccines in 2017 and 2018; however, no significant differences were noted in 2019 (Table 2).

Table 3 summarizes the IRs of different AEFI symptoms, according to the type of the EV71 vaccine. In total, 1577 AEFI symptoms were reported after administration of the EV71 vaccines. The IRs of different symptoms ranged from 0.1 to 18.1 (per 100,000 doses) for the H2 cell-based EV71 vaccine and from 0.1 to 46.1 (per 100,000 doses) for the Vero cell-based EV71 vaccine. For both types of EV71 vaccines, the top five systemic symptoms were fever, irritability, allergic eruptions, fatigue, and loss of appetite. Redness and induration were the main symptoms at the injection site. More than 93% of the rare adverse reactions corresponded to allergic eruptions. More than 85% of AEFIs occurred between 30 min and 3 days after administration for both type of EV71 vaccine(Table 4). All AEFIs were resolved without requiring special medical care.

4. Discussion

In the current study, the reported IRs for AEFI was evaluated based on a passive post-marketing AEFI surveillance system and EIRS. The EV71 vaccine was not administered as part of the EPI in China, parents need to pay for administration of this vaccine. Thus, the number of doses of the EV71 vaccine administered during the first use 3 years of use has varied. In this study, the number of doses administered was only about 350,000 doses in the first year of introduction; however, in 2018, which was the second year of administration, the number increased to about 845,000 doses. Therefore, in this study, we calculated and compared the IRs of AEFIs related to administration of the EV71 vaccine based on CNAEFI and EIRS data.

The IRs of AEFIs related to administration of the EV71 vaccines ranged from 48.2 to 59.2 per 100,000 doses in the first use 3 years of administration in the Jiangsu Province. Moreover, the AEFI IR of boys was higher than that of girls, consistent with other China's vaccine AEFI studies [31,32]. Most AEFIs occurred in patients 1–2 years of age, this may be because children's immune system response and tolerance increases with age, some adverse reactions

Table 1
Characteristics of AEFIs after EV71 vaccination in Jiangsu Province, China from 2017 to 2019.

		2017			2018			2019		
		Vaccine doses	AEFI cases	IR (per 100,000 doses)	Vaccine doses	AEFI cases	IR (per 100,000 doses)	Vaccine doses	AEFI cases	IR (per 100,000 doses)
Sex	Male	186,276	109	58.5	439,305	237	53.9	321,440	206	64.1
	Female	167,035	100	59.9	405,730	170	41.9	313,439	138	44.0
Age Group	6 months-1 yrs	82,720	39	47.1	210,812	110	52.2	225,827	127	56.2
	1–2 yrs	140,083	105	75.0	331,724	182	54.9	239,566	169	70.5
	2–3 yrs	76,734	45	58.6	155,116	76	49.0	99,012	24	24.2
	≥3yrs	53,774	20	37.2	147,383	39	26.5	70,474	24	34.1
Dose	First Dose	202,180	148	73.2	457,028	283	61.9	339,094	213	62.8
	Second Dose	151,131	61	40.4	388,007	124	32.0	295,785	131	44.3
Vaccine Type	H2 cell-based	244,781	104	42.5	569,424	227	39.9	398,445	207	52.0
	Vero cell-based	108,530	105	96.7	275,611	180	65.3	236,434	137	57.9
Total		**353,311**	**209**	**59.2**	**845,035**	**407**	**48.2**	**634,879**	**344**	**54.2**

Table 2
Classification of AEFIs incidence rates following EV71 vaccination in Jiangsu Province, China from 2017 to 2019.

Classification of AEFIs	2017					2018					2019				
	H2 cell-based		Vero cell-based			H2 cell-based		Vero cell-based			H2 cell-based		Vero cell-based		
	AEFI cases (%)	IR (per 100,000 doses)	AEFI cases (%)	IR (per 100,000 doses)	IRR (95%CI)	AEFI cases (%)	IR (per 100,000 doses)	AEFI cases (%)	IR (per 100,000 doses)	IRR (95%CI)	AEFI cases (%)	IR (per 100,000 doses)	AEFI cases (%)	IR (per 100,000 doses)	IRR (95%CI)
Common reaction	87 (84.5)	35.5	91 (87.5)	83.8	0.42 (0.32–0.57)	198 (86.5)	34.8	160 (88.9)	58.1	0.60 (0.49–0.74)	177 (85.5)	44.4	119 (86.9)	50.3	0.88 (0.70–1.11)
Rare reaction	16 (15.5)	6.5	12 (11.5)	11.1	0.59 (0.28–1.25)	24 (10.5)	4.2	19 (10.6)	6.9	0.61 (0.34–1.12)	30 (14.5)	7.5	16 (11.7)	6.8	1.11 (0.61–2.04)
Coincidental event	1(1.0)	0.4	2(1.9)	1.8	0.22 (0.02–2.45)	5(2.2)	0.9	1(0.6)	0.4	2.42 (0.28–20.72)	0(0)	0	2(1.5)	0.8	0.14*

*P value of Fisher's exact test.

Table 3
AEFIs symptoms after EV71 vaccination in Jiangsu Province, China from 2017 to 2019.

AEFIs symptoms		H2 cell-based		Vero cell-based	
		Number(%)	IR (per 100,000 doses)	Number(%)	IR(per 100,000 doses)
Systemic reaction	Fever (≥38.6 °C)	220(30.6)	18.1	286(33.3)	46.1
	Fever (37.6 °C-38.5 °C)	114(15.9)	9.4	154(17.9)	24.8
	Fever (37.1 °C-37.5 °C)	6(0.8)	0.5	17(2.0)	2.7
	Irritability	100(13.9)	8.2	119(13.9)	19.2
	Allergic eruption	65(9.1)	5.4	44(5.1)	7.1
	Fatigue	53(7.4)	4.4	44(5.1)	7.1
	Loss of appetite	51(7.1)	4.2	65(7.6)	10.5
	Drowsiness	19(2.6)	1.6	22(2.6)	3.5
	Vomiting	18(2.5)	1.5	36(4.2)	5.8
	Diarrhea	17(2.4)	1.4	16(1.9)	2.6
	Pruritus	16(2.2)	1.3	12(1.4)	1.9
	Cough	5(0.7)	0.4	1(0.1)	0.2
	Sweat	5(0.7)	0.4	2(0.2)	0.3
	Rhinorrhea	4(0.6)	0.3	2(0.2)	0.3
	Nausea	2(0.3)	0.2	9(1.0)	1.5
	Headache	2(0.3)	0.2	1(0.1)	0.2
	Skin pale	2(0.3)	0.2	1(0.1)	0.2
	Abdominal pain	1(0.1)	0.1	2(0.2)	0.3
	Dizzy	1(0.1)	0.1	3(0.3)	0.5
	Congestion in throat	1 (0.1)	0.1	4(0.5)	0.6
Injection site reactions	Redness	11(1.5)	0.9	9(1.0)	1.5
	Induration	5(0.7)	0.4	10(1.2)	1.6

Table 4
Time intervals between EV71 vaccination and reporting of AEFIs in Jiangsu Province, China from 2017 to 2019.

AEFIs time intervals	H2 cell-based		Vero cell-based	
	Number(%)	IR (per 100,000 doses)	Number(%)	IR (per 100,000 doses)
≤30 min	53(9.9)	4.4	45(10.7)	7.3
30 min −3 days	470(87.4)	38.8	369(87.4)	59.5
≥3 days	15(2.8)	1.2	8(1.9)	1.3

can be more easily recognized and reported in older children, consistent with the findings of other studies on vaccine-induced AEFIs [16,17]. In this study, the IR of AEFI was higher after the first dose than after the second dose, as previously reported in active safety surveillance studies of the EV71 vaccines [18,19].

This study was a passive analysis based on CNAEFIS routine surveillance, the limitations of passive AEFI surveillance include over- and under-reporting, biased reporting, and inconsistency in the quality and completeness of reports among other studies [20]. VCs doctors or children's parents may not be aware and thus may not report less serious adverse reactions. Therefore, the IRs of AEFIs in this study may be much lower than that in previous clinical trials [21,22]. However the types of AEFI symptoms related to EV71 vaccines were consistent with previous pre-marketing studies [23,24]; the most commonly reported AEFIs symptoms were fever, irritability, allergic eruption, fatigue, loss of appetite, redness and induration at the injection site.

Regarding the differences in AEFI classification, our study showed a decreased trend for the Vero cell-based EV71 vaccine. In particular, in 2017 and 2018, the IR of AEFIs considered common reactions was slightly higher for the Vero cell-based EV71 vaccine than for the H2 cell-based EV71 vaccine. Nevertheless, no differences in rare reactions and coincidental events were found between the two vaccines. Before approval of the Vero cell-based EV71 vaccine in China, a large-scale clinical trial was performed in Jiangsu Province, China [23,25]. During the first 2 years of approval, the VC doctors were more wary of the Vero cell-based EV71 vaccine safety, and more common reactions were reported to routine AEFI surveillance systems. However, for rare reactions and coincidental events, investigation and diagnosis were required by the VC doctor, and the conclusions were carefully considered to ensure accuracy. Therefore, the IR of common reactions was shown higher for the Vero cell-based EV71 vaccine than the H2 cell-based vaccine during the first 2 years. Briefly, these findings suggested there were no significant differences in AEFI classifications between the two EV71 vaccines.

A prior clinical trial indicated that adverse reactions to the EV71 vaccine were mainly developed within 7 days after administration. In this study, most AEFIs were developed between 30 min and 3 days after administration. This may be because the awareness in parents or guardians decreased over time, and some mild adverse reaction may have appeared but not been reported after 3 days. A similar phenomenon was also observed in a post-marketing study of other vaccines [26,27]. Hence, we concluded that the time interval for the occurrence of AEFIs related to the EV71 vaccine was identical to that in pre-marketing clinical trials.

One limitation of this study was the use of a passive reporting system for analysis of AEFIs; this system could lead to inconsistencies in data quality, related to the capability of the VC doctors, the awareness of parents or guardians, and the perception of vaccine safety [28,29]. Thus, some AEFIs may have not been accurately reported, and additional active surveillance studies are needed to confirm and validate our findings in the future.

In conclusion, our findings demonstrated that most AEFIs that occurred following administration of the EV71 vaccine from 2017 to 2019 were mild and common reactions; no new or unexpected safety signals were reported during the surveillance period. Both types of EV71 vaccines showed satisfactory safety profiles in the target population, and no significant differences in rare reactions between the two type of EV71 vaccines were observed. The AEFI profiles reported in this study were identical to those in pre-marketing clinical trials. Further studies are needed to actively assess safety.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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